REMARKS

Claim 1, as amended, and claims 3, 7, 17, 19, and 22 are pending in the instant application. No new matter has been added as a result of the above-described amendments. The rejections set forth in the Office Action have been overcome by amendment or are traversed by argument below.

1. Rejection of claims 1 and 17 under 35 U.S.C. § 102

The Office Action maintains a rejection of claims 1 and 17 under 35 U.S.C. § 102(b), as being anticipated by International Publication No. WO 95/22626 (Meijer *et al.*). Applicants' understanding of this rejection is fully set forth in Applicants' response to the Office Action mailed April 5, 2005.

Applicants have amended claim 1 to recite a reagent comprising a plurality of genomic HPV DNA probe sets in which at least six of the probe sets comprise a plurality of nucleic acid fragments having different nucleotide sequences that detectably hybridize to a plurality of different nucleotide sequences of essentially the full-length genomic sequence of HPV types 16, 18, 31, 33, 35, or 51. Applicants contend that the reagent recited in amended claim 1 does not encompass the oligonucleotide cocktail disclosed by Meijer *et al.*

As discussed in Applicants' response to the Office Action mailed April 5, 2005, Meijer *et al.* disclose oligonucleotide primers of only 23-28 nucleotides for amplifying HPV DNA present in a sample by polymerase chain reaction, and oligonucleotide probes of only 30 nucleotides for HPV genotyping of the amplification product. The reagent of claim 1, on the other hand, comprises a plurality of genomic HPV DNA probe sets, wherein each probe set comprises a plurality of nucleic acid fragments having different nucleotide sequences that detectably hybridize to a plurality of different nucleotide sequences of essentially the full-length genomic sequence of HPV types 16, 18, 31, 33, 35, or 51. Because each of the type-specific oligonucleotide probes present in the Meijer *et al.* cocktail comprises a plurality of nucleic acid fragments having identical nucleotide sequences, the oligonucleotide probes disclosed by Meijer et al. would ***not*** comprise a plurality of nucleic acid fragments having different nucleotide sequences. In addition, because the oligonucleotide probes disclosed by Meijer *et al.* correspond to a small portion of the entire HCV genome (about 0.38%), the oligonucleotide probes disclosed by Meijer et al. would ***not*** hybridize to a plurality of different

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nucleotide sequences of essentially the full-length genomic sequence of any HPV type.

Applicants contend that because Meijer *et al.* do not disclose a reagent comprising a plurality of genomic HPV DNA probe sets in which at least six of the probe sets comprise a plurality of nucleic acid fragments having different nucleotide sequences that detectably hybridize to a plurality of different nucleotide sequences of essentially the full-length genomic sequence of HPV types 16, 18, 31, 33, 35, or 51, Meijer *et al.* cannot anticipate claims 1 and 17. Withdrawal of this rejection is therefore respectfully solicited.

2. Rejections of claims 3 and 19 under 35 U.S.C. § 103

a. Rejection of claims 3 and 19 as being unpatentable over Meijer *et al.* in view of Orth *et al.*

The Office Action maintains a rejection of claims 3 and 19 under 35 U.S.C. § 103(a), as being unpatentable over International Publication No. WO 95/22626 (Meijer *et al.*) in view of U.S. Patent No. 5,981,173 (Orth *et al.*). Applicants' understanding of this rejection is fully set forth in Applicants' response to the Office Action mailed April 5, 2005.

As discussed in section 1 above, Meijer *et al.* do not disclose a reagent comprising a plurality of genomic HPV DNA probe sets, wherein each probe set comprises a plurality of nucleic acid fragments having different nucleotide sequences that detectably hybridize to a plurality of different nucleotide sequences of essentially the full-length genomic sequence of any HPV type. Because Orth *et al.* disclose oligonucleotide probes for the detection of HPV types 68 and 70, Orth *et al.* also do not disclose a reagent comprising a plurality of genomic HPV DNA probe sets, wherein each probe set comprises a plurality of nucleic acid fragments having different nucleotide sequences that detectably hybridize to a plurality of different nucleotide sequences of essentially the full-length genomic sequence of any HPV type. Applicants contend that because an oligonucleotide cocktail comprising the oligonucleotide probes disclosed by Meijer *et al.* and Orth *et al.* does not comprise a plurality of genomic HPV DNA probe sets, wherein each probe set comprises a plurality of nucleic acid fragments having different nucleotide sequences that detectably hybridize to a plurality of different nucleotide sequences of essentially the full-length genomic sequence of any HPV type, Meijer *et al.* in view of Orth *et al.* does not result in a *prima facie* case of obviousness with respect to

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claims 3 and 19. Withdrawal of this rejection is therefore respectfully solicited.

b. Rejection of claims 7 and 22 as being unpatentable over Meijer *et al.* in view of Bauer *et al.*

The Office Action also maintains a rejection of claims 7 and 22 under 35 U.S.C. § 103(a), as being unpatentable over International Publication No. WO 95/22626 (Meijer *et al.*) in view of U.S. Patent No. 5,639,871 (Bauer *et al.*). Applicants' understanding of this rejection is fully set forth in Applicants' response to the Office Action mailed April 5, 2005.

As discussed in section 1 above, Meijer *et al.* do not disclose a reagent comprising a plurality of genomic HPV DNA probe sets, wherein each probe set comprises a plurality of nucleic acid fragments having different nucleotide sequences that detectably hybridize to a plurality of different nucleotide sequences of essentially the full-length genomic sequence of any HPV type. Applicants contend that because an oligonucleotide cocktail comprising the oligonucleotide probes disclosed by Meijer *et al.* and optimized according to the teachings of Bauer *et al.* does not comprise a plurality of genomic HPV DNA probe sets, wherein each probe set comprises a plurality of nucleic acid fragments having different nucleotide sequences that detectably hybridize to a plurality of different nucleotide sequences of essentially the full-length genomic sequence of any HPV type, Meijer *et al.* in view of Bauer *et al.* does not result in a *prima facie* case of obviousness with respect to claims 7 and 22. Withdrawal of this rejection is therefore respectfully solicited.

c. Rejection of claims 1, 3, 17, and 19 as being unpatentable over Nuovo *et al.* in view of Cox *et al.*

The Office Action maintains a rejection of claims 1, 3, 17, and 19 under 35 U.S.C. § 103(a), as being unpatentable over Nuovo *et al.*, 1995, *J. Histotechnology* 18:105-110 in view of Cox *et al.*, 1995, *Am. J. Obstet. Gynecol.* 172:946-54. Applicants' understanding of this rejection is fully set forth in Applicants' response to the Office Action mailed April 5, 2005.

Applicants note that an analysis of obviousness must be based on the following factual inquiries: (1) the scope and content of the prior art; (2) the differences between the prior art and the claims at issue; (3) the level of ordinary skill in the art at the time the invention was made; and (4)

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objective evidence of nonobviosuness, if any. *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966). Moreover, where claimed subject matter has been rejected as obvious in view of a combination of prior art references, a proper analysis under § 103 *also requires* consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and (2) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success. *In re Vaeck*, 947 F.2d 488, 493 (Fed. Cir. 1991). As the Federal Circuit has emphasized: "[b]oth the suggestion and the reasonable expectation of success must be founded in the prior art, not the Applicants' disclosure." *Id.*

Applicants respectfully disagree with the Action's assertion that Nuovo *et al.* in view of Cox *et al.* results in a *prima facie* case of obviousness with respect to claims 1, 3, 17, and 19. In particular, Applicants disagree with both the Action's improper characterization of the Nuovo *et al.* reference and the Action's improper combination of Nuovo *et al.* and Cox *et al.* to establish its *prima facie* case of obviousness. Nuovo *et al.* describes the use of eight different HPV probe kits, four of which were obtained from Digene Diagnostics (Silver Spring, MD) and four of which were obtained from ONCOR (Gaithersburg, MD) (page 106). Both Digene Diagnostics and ONCOR provided HPV probe kits – referred to as Omniprobe and the wide spectrum probe cocktail, respectively – that were capable of detectably hybridizing to the sequence of HPV types 6, 11, 16, 18, 31, 33, 35, 42, 43, 44, 45, and 51 (page 106). Since each of these probe kits was capable of detectably hybridizing to the sequence of low-risk HPV types 6 and 11, both of these kits would detectably hybridize to the genomic sequence of a low-risk HPV type. Because the prior art references being combined must teach or suggest all of a claim's limitations (M.P.E.P. § 2142), the use of either Digene Diagnostics' Omniprobe or ONCOR's wide spectrum probe cocktail to establish a *prima facie* case of obviousness with respect to claims 1, 3, 17, and 19 would be improper.

Nuovo *et al.* also describe the use of probe kits for specific HPV types (page 106). Specifically, Nuovo *et al.* describe the use of three ***separate*** probe kits, obtained from both Digene Diagnostics and ONCOR, which contain probes for ***either*** (1) HPV types 6 and 11; (2) HPV types 16 and 18; ***or*** (3) HPV types 31, 33, and 35 (page 106). Since the probe kits obtained from ONCOR were generated from specific subgenomic areas in order to minimize crosshomology with other

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known HPV types (page 106), none of the ONCOR probe mixes comprises a plurality of nucleic acid fragments having different nucleotide sequences that detectably hybridize to ***a plurality of different nucleotide sequences of essentially the full-length genomic sequence*** of HPV types 16, 18, 31, 33, 35, or 51 (in addition, the probe kit for HPV types 6 and 11 would detectably hybridize to the genomic sequence of a low-risk HPV type). Because the prior art references being combined must teach or suggest all of a claim's limitations (M.P.E.P. § 2142), the use of ONCOR's type-specific probe kits to establish a *prima facie* case of obviousness with respect to claims 1, 3, 17, and 19 would be improper.

With regard to Digene Diagnostics' type-specific probe kits, the probe kit for HPV types 6 and 11 would detectably hybridize to the genomic sequence of a low-risk HPV type, the probe kit for HPV types 16 and 18 would ***not detectably*** hybridize to a plurality of different nucleotide sequences of essentially the full-length genomic sequence of HPV types 33, 35, and 51 as required by independent claim 1, and the probe kit for HPV types 31, 33, and 35 would ***not detectably*** hybridize to a plurality of different nucleotide sequences of essentially the full-length genomic sequence of HPV type 18 as required by independent claim 1. Moreover, Nuovo *et al.* would have recognized that the probe sets for HPV types 16/18 and 31/33/35 were each incapable of detectably hybridizing to a plurality of different nucleotide sequences of essentially the full-length genomic sequence of the HPV types recited in independent claim 1 ***only*** by considering Applicants' teachings (specifically, the teachings on pages 8-9 of Applicants' specification). Because the teaching or suggestion to make the claimed combination must be found in the prior art, and not in Applicants' disclosure (*In re Vaeck*, 947 F.2d at 493; M.P.E.P. § 2143.01), the use of Digene Diagnostics' type-specific probe kits to establish a *prima facie* case of obviousness with respect to claims 1, 3, 17, and 19 would be improper.

The Action attempts to cure the deficiencies and limited disclosure of Nuovo *et al.* by combining the teachings of this reference with those of the Cox *et al.* reference. The Action's assertion that one of ordinary skill in the art, in view of the Nuovo *et al.* and Cox *et al.* disclosures, would know to make the claimed reagent appears to be based on (1) the disclosure in Nuovo *et al.* of two reagents comprising genomic HPV DNA probe sets for HPV types 16 and 18 and for HPV types 31, 33, and 35 (p. 106); (2) the disclosure in Cox *et al.* of a hybrid capture method using a reagent

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comprising RNA probes for HPV types 16, 18, 31, 33, 35, 45, 51, and 52 (p. 948); and (3) the knowledge of one of ordinary skill in the art that genomic HPV DNA probes would be more stable in solution than RNA probes. Because the Action uses improper hindsight reasoning to combine Nuovo *et al.* and Cox *et al.*, and more importantly, because the Action has not pointed to a teaching or suggestion to make the claimed reagent in the prior art, the combination of these references is improper.

Applicants contend that the reasoning set forth in the Action is improper and clearly contravenes the Federal Circuit's requirement that the teaching or suggestion to make the claimed combination must be found in the prior art (*In re Vaeck*, 947 F.2d at 493; M.P.E.P. § 2143.01). Applicants also contend that absent Applicants' teachings, neither Nuovo *et al.* nor Cox *et al.* would have appreciated the benefits of using the claimed reagent; namely, that a reagent comprising only six high-risk genomic HPV DNA probe sets would allow for the detection of at least thirteen high-risk HPV types without cross-reacting with low-risk HPV types. Furthermore, Applicants contend that one of ordinary skill in the art would ***not*** know to substitute the ***RNA*** probes of the hybrid capture method disclosed by Cox *et al.* with ***genomic DNA*** probes because the latter would simply not work. In the hybrid capture method disclosed by Cox *et al.*, single-stranded DNA isolated from a cell sample is allowed to hybridize to RNA probes corresponding to a number of high-risk HPV types, and RNA/DNA hybrids that form are immobilized in a capture tube coated with antibodies ***specific for RNA/DNA hybrids*** (p. 948). Since the use of a reagent comprising RNA probes is a necessary requirement of the method disclosed by Cox *et al.*, one of ordinary skill would not, as the Action suggests, substitute the RNA probes of this method with genomic DNA probes. The relative stability of RNA and genomic DNA probes would simply not be a relevant consideration.

Thus, absent Applicants' teachings, Nuovo *et al.* would not have thought to mix the Digene Diagnostics' type-specific probe kits for HPV types 16/18 and 31/33/35 to detect more than the five high-risk HPV types that comprised these separate genomic probe cocktails. In addition, Cox *et al.* would not have considered preparing DNA - rather than RNA - capture probes, since the former would simply not function in hybrid capture protocol. Finally, one of ordinary skill in the art would not have thought to recreate the RNA probe cocktail of Cox *et al.* using genomic DNA probes because, absent Applicants' teachings, the skilled artisan would not understand that a reagent

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comprising only six high-risk genomic HPV DNA probe sets would allow for the detection of at least thirteen high-risk HPV types without cross-reacting with low-risk HPV types, and therefore, would not understand how the claimed reagent provided any improvement over the Digene Diagnostics' type-specific probe kits described in Nuovo *et al.* Applicants contend that for the reasons listed above, Nuovo *et al.* in view of Cox *et al.* does not result in a *prima facie* case of obviousness with respect to claims 1, 3, 17, and 19. Withdrawal of this rejection is therefore respectfully solicited.

3. Provisional rejection of claims 1, 3, 7, 17, 19, and 22 for obviousness-type double patenting

The Action asserts a provisional rejection of claims 1, 3, 7, 17, 19, and 22 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-7 and 17-22 of U.S. Application No. 10/646,633.

Applicants acknowledge the rejections under the doctrine of obviousness-type double patenting, and elect to address these grounds of rejection by submitting a Terminal Disclaimer or by argument upon notification that all other conditions for patentability have been met, and the claims are otherwise in condition for allowance.

CONCLUSIONS

Applicants respectfully contend that all conditions of patentability are met in the pending claims as amended. Allowance of the claims is thereby respectfully solicited.

If Examiner Switzer believes it to be helpful, she is invited to contact the undersigned representative by telephone at 312-913-0001.

Respectfully submitted,
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